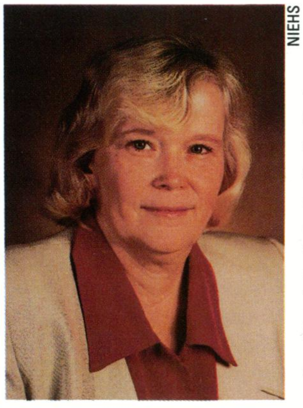
NIEHS investigators have developed sensitive assays to detect susceptibility to carcinogens in cigarette smoke, foods, industrial by-products, and environmental pollution. Based on tests of more than 1000 individuals for these susceptibility genes, the frequency of the at-risk genotypes vary significantly among Asians, Caucasians, and African-Americans. Such variation suggests that some of the differences in cancer incidence among ethnic groups may be due to genetic differences as well as exposure differences.

In collaboration with Jack Taylor of the NIEHS Epidemiology Branch, LBRA is testing the effect of certain cancer susceptibility genes in studies of bladder cancer, lung cancer, and liver cancer. Individuals who carry the at-risk genotype for glutathione transferase μ, an enzyme that detoxifies constituents of cigarette smoke, suffer a 70% increased risk of bladder cancer. In ongoing studies with researchers at the National Cancer Institute, Columbia University, University of North Carolina, and University of Keele, England, NIEHS is exploring how genetic variability in the metabolism of carcinogens affects risk for cancer of the bladder, lung, liver, stomach, colon, head, and neck.

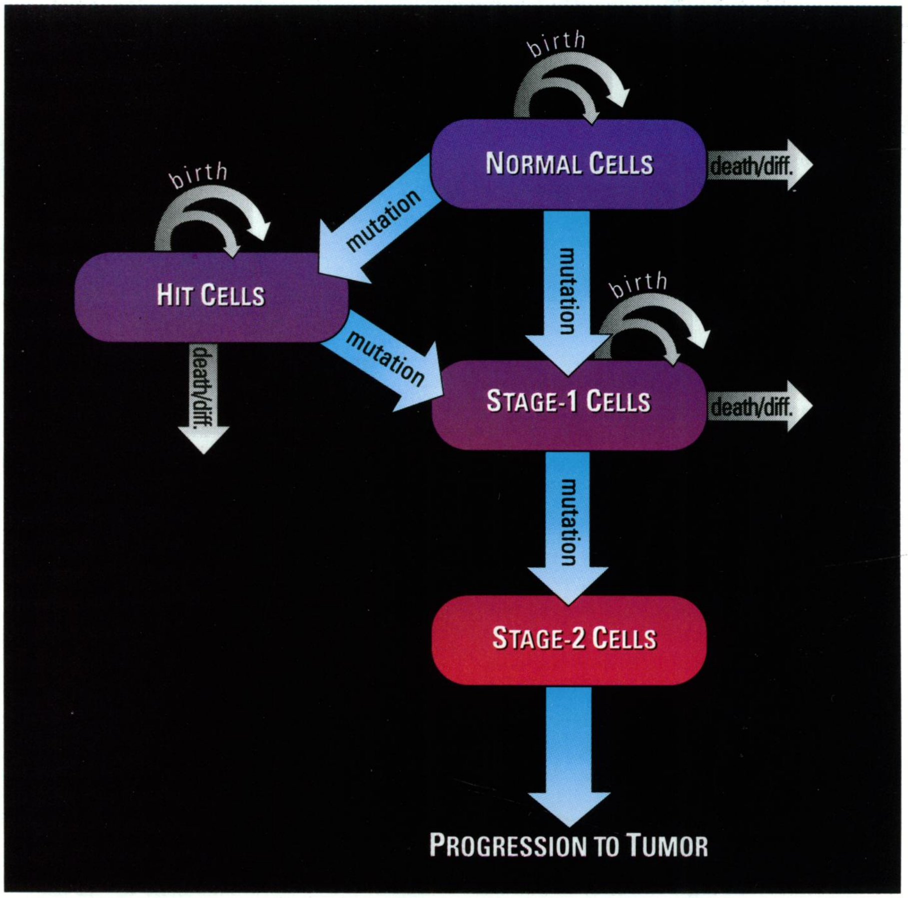
The cytochrome P450 enzymes catalyze the oxidation of drugs, carcinogens, and other xenobiotics. Joyce Goldstein's group in LBRA is looking for genetic defects in these enzymes that affect the ability of humans to metabolize chemical agents. Population studies have shown that some people are poor metabolizers of the drug *S*-mephenytoin, and defective metabolism is inherited. Metabolism of other drugs, including barbiturates, the antimalarials, and the antiulcer drug omeprazole, may be mediated by the same enzyme. Goldstein's group has isolated two new genes in the P450 subfamily. These studies use conventional cloning techniques and polymerase chain reaction to identify genetic differences in genes from poor or extensive metabolizers of the drugs. The ability of proteins coded by these genes to metabolize drugs and chemicals is being studied by Burhan Ghanayem of LBRA.



Joyce Goldstein—isolating P450 genes

Laboratory of Quantitative and Computational Biology

High-speed computing, the improved ability to collect a broad range of data at the biochemical and molecular levels, and recent advances in mathematics and statistics have significantly enhanced the utility of mathematical modeling in describing and studying environmental risks. The emergence of these new technologies requires a multidisciplinary approach in the quantitative sciences and creates the need for research teams in quantitative and computational areas. To address this need, NIEHS is creating a new laboratory, the Laboratory of Quantitative and Computational Biology (LQCB). The primary responsibility of LQCB is to investigate the application of mathematics, statistics, computational chemistry, electrical engineering, and computer science to the understanding of human health risks from exposure to environmental agents. LQCB will initially combine scientists from three research groups at NIEHS: a group developing new methodology and applying existing methodology to the application of quantum and statistical mechanics in environmental health, a group focusing on research in mathematical modeling aimed at developing new methodologies for risk estimation, and the NIEHS Scientific Computing Laboratory, whose primary purpose is computational support and direction for intramural research at NIEHS. In addition to these scientists, the LQCB plans to add expertise in a variety of related fields, including artificial intelligence and virtual reality. LQCB will be able to model biological mechanisms at all levels of complexity from molecular to demographic. The collaboration of LQCB and other NIEHS branches will lead to more efficient use of NIEHS resources through improved experimental design and the formal use of data from multiple sources. Current research and short-term research plans for the LQCB can be divided into seven broad areas: carcinogenic modeling, molecular modeling, biochemical and pharmacological modeling, modeling noncarcinogenic endpoints, computer science, artificial intelligence, and risk communication. Christopher Portier will be acting chief of this new laboratory.



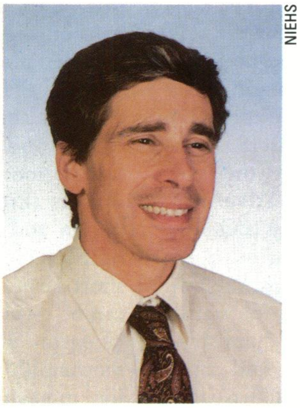
A clonal two-path/two-stage model of carcinogenesis is being developed by members of the LQCB.

Challenging a Dioxin Hypothesis

Dioxin is believed by many to be one of the most potent carcinogens in the environment. Emerging information at the molecular level concerning the mechanism of dioxin's toxicity has reignited controversy regarding safe exposure levels for dioxin and prompted the reassessment by the EPA. As part of these efforts, scientists at NIEHS developed mechanistic models to challenge the dioxin threshold hypothesis.

At the heart of the dioxin controversy is a proposed hypothesis that toxic effects of dioxin are receptor mediated, and at sufficiently low exposure to dioxin (i.e., a threshold), too few receptors would be occupied to produce a significant biological consequence. Researchers Christopher Portier and Michael Kohn of the Laboratory of Quantitative and Computational Biology, in collaboration with the Laboratory of Biochemical Risk Analysis and the Biostatistics Department of the German Cancer Research Center, used data on the effects of dioxin, including tissue concentrations, changes in expression of liver proteins, modification of plasma membrane epidermal growth factor, interactions with estrogens, cellular proliferation, and carcinogenesis, to create a comprehensive mechanistically based model of dioxin's effects.

Portier and Kohn found that although the classical receptor-mediated models theoretically allowed for both nonlinear behavior that mimics a threshold and linearity at low doses, these models failed to predict a nonlinear relationship at low doses. The models predict that binding of dioxin to the Ah receptor follows linear kinetics at low doses, and induction of the Ah receptor by the dioxin-Ah receptor complex does not alter this curvature. Binding of dioxin to other liver proteins does not seem to significantly affect the dose–response curve for expression of any of the proteins modeled. Not only were the NIEHS models unable to detect any nonlinearity in cell kinetics, they also indicated that dioxin potentially produces premalignant lesions in the liver.



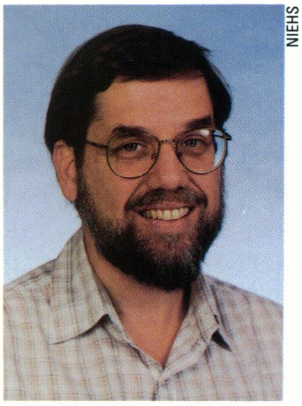
NIEHS

Michael Kohn—modeling effects of dioxin

Because changes in gene expression do not necessarily predict toxicity, current studies are attempting to develop dose–response models to determine if the toxic effects of dioxin exhibit linear or nonlinear behavior. For example, Portier and Kohn have undertaken a theoretical analysis of the impact of receptor-based models on the shape and magnitude of tumor incidence rates.

EPA Reevaluation of Dioxin's Risks

In 1991, then EPA administrator William Reilly initiated a reevaluation of dioxin's risks. George Lucier and Christopher Portier have been involved in this reevaluation in a number of ways. Lucier and Michael Gallo (EOHSI) co-chair the committee that prepared the dose–response models chapter, the cornerstone of the reevaluation. Portier played a key role in the development of biologically based dose–response models for dioxin's effects. Lucier also prepared the chapter on animal carcinogenicity. The dose–response models and animal carcinogenicity chapters received favorable reviews from the EPA Peer Review process in September 1992. The Scientific Advisory Board will review the background papers and the risk characterization in late 1993.



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Ronald Melnick—modeling butadiene

Species Differences in Butadiene Carcinogenesis

1,3-Butadiene, a gaseous hydrocarbon used in the production of synthetic rubber and other resins, is a carcinogen in rodents and is associated with leukemia and lymphoma in humans. Mice develop tumors at lower exposures to butadiene than rats. Recent studies have shown that mice have a higher capacity to oxidize butadiene to 1,2-epoxy-3-butene, a mutagenic and carcinogenic compound, than either rats or humans. Some investigators have concluded that species differences in tumor development are due to differences in metabolic activation of butadiene and detoxification of expoxide intermediates.

To validate this conclusion, two NIEHS scientists, Michael Kohn and Ronald Melnick, constructed physiologically based pharmacokinetic models of the distribution and clearance of inhaled butadiene in mice, rats, and humans. In contrast to the conclusions of earlier investigators, the models predict that species differences in the uptake of butadiene and the blood concentration of epoxybutene are much more sensitive to the physiological parameters (e.g., ventilation rate and cardiac output) than to the biochemical parameters. In addition, the model predicts that, because of these physiological differences, butadiene accumulates in the fat of humans, but not mice, on repeated exposure. According to the model, butadiene released from fat during the periods between exposures continues to be converted into epoxybutene, adding to the carcinogenic risk.

In a recent editorial in *Science*, it was stated that after exposure to 10 ppm butadiene in the ambient air, blood epoxybutene levels are 590 times higher in mice than in monkeys. Yet, in Kohn and Melnick's models, mice produce only 5.5 times as much epoxybutene as humans at exposures that result in equivalent amounts of butadiene absorbed into the body. Risk assessments of inhaled carcinogens are normally performed on the basis of internal dose rather than on the basis of atmospheric concentration. Inhalation studies can lead to different implications relevant to human risk depending on the manner in which the results are reported.

Computed epoxybutene concentrations, by themselves, were found not to correlate with tumor incidence in mice and rats. Rats exposed to 1000 ppm butadiene generate about twice the concentration of epoxybutene in lung as mice exposed to 60 ppm. Yet mice develop lung tumors under those conditions and rats do not. Kohn and Melnick conclude that other biochemical processes (e.g., formation of DNA adducts, efficiency of DNA repair) not included in their models are more important determinants of the differential response of the two species than the concentration of the putative carcinogen.

Risk Assessment Seminar Series

As an adjunct to its initiatives in risk assessment, NIEHS is hosting a seminar series featuring prominent scientists in the risk assessment field. The first seminar was June 8, with Christopher Portier, chief of the NIEHS Laboratory of Quantitative and Computational Biology. Other speakers in the series will include David P. Rall, internationally recognized environmental health researcher and retired director of NIEHS; Joe Rodricks of Environ, a Washington, DC firm; John Graham of the Harvard Institute of Risk Assessment; William Farland and John Vandenberg of U.S. EPA; Henry Falk of CDC; Ellen Silbergeld of the University of Maryland at Baltimore and the Environmental Defense Fund; Leslie Staynor of NIOSH; Gil Omenn of the University of Washington; and Roger McClellan of the Chemical Industry Institute of Toxicology.

The series is designed to allow professionals in risk assessment to discuss critical issues. For information on the series contact George Lucier, (919) 541-3802.